HFA-305

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

0300 '00 FEB 22 A9:44

February 18, 2000

Mr. Paul F. Manley
Johnson & Johnson
World Wide Director, Regulatory Affairs
199 Grandview Road
Skillman, New Jersey 08558-9418

Dear Mr. Manley:

I am writing in response to your letter of September 23, 1999 to Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research (CDER) expressing your concerns with the Food and Drug Administration's (FDA) support of a proposal to allow manufacturers to substitute skin tape stripping for pharmacodynamic measurements or comparative clinical trials. I apologize for the delay in responding to your letter

Thank you for taking the time to write to the FDA to express your interest and comments on this subject. You can be sure that the Agency will continue to base any decision on sound science.

As you know, on June 18, 1998, the FDA published a Federal Register Notice announcing the availability of a guidance for industry entitled, "Draft Guidance for Industry on Topical Dermatological Drug Product NDA's and ANDA's -- In Vivo Bioavailability, Bioequivalence, In Vitro Release and Associated Studies." This draft guidance is intended to provide recommendations to sponsors of new drug applications (NDA's), abbreviated new drug applications (ANDA's), and supplements who intend to perform bioavailability and bioequivalence studies for topically applied dermatological drug products during either the preapproval or postapproval period. The FDA welcomes comments from the drug industry, and I have forwarded a copy of your letter to the Dockets Management Branch for inclusion in the docket (Docket No. 98D-0388).

Thank you for writing. Please do not hesitate to contact us again if you have further questions or comments.

Sincerely,

Theresa M. Martin
Executive Secretariat Staff (HFD-6)
Center for Drug Evaluation and Research

98D-0388

C20 /AN

cc: HFA-305 (w/copy of incoming)
HFD-3/Sherwood

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Concur:KBongiovanni:02/17/00

Johnson & Johnson
CONSUMER COMPANIES, INC.

SEP 23 1999

Janet Woodcock, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
HFD-001, WOC2, Room 6027
5600 Fishers Lane
Rockville, MD 20857

GENERAL CORRESPONDENCE

Topical Dermatological Drug Product NDAs and ANDAs – In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies

Dear Ms. Woodcock:

In June 1998, FDA published in the Federal Register a guidance for Industry in draft form titled "Topical Dermatological Drug Product NDAs and ANDAs – In Vivo, Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies (the "Draft Guidance"). In the Draft Guidance, FDA proposed to permit generic companies to use a method, called dermatopharmacokinetics (DPK), commonly referred to as tapestripping, to demonstrate bioequivalence ("BE") between a generic topical product and the innovator topical products. In addition, FDA proposed that where the generic manufacturer seeks approval for lower strengths of the product involved, an in vitro release method may be used to demonstrate BE. We understand, based upon representations by FDA officials, that FDA intends to finalize the Draft Guidance without material changes, despite significant concerns raised by Industry and certain FDA officials that these methods of demonstrating BE have not been sufficiently validated and have never been adequately correlated to clinical outcomes.

We understand that FDA has great latitude in determining methods that can be used to establish BE. Those methods, however, must be reasonably and scientifically supported as appropriate surrogates for demonstrating comparable safety and efficacy between the generic product and the innovator; that is, that the products will truly be bioequivalent. See Schering Corp. v. Sullivan, 782 F. Supp. 645, 651 (D.D.C. Jan. 17, 1992). In this case, there is no scientific consensus that either tape stripping or in vitro release have been adequately demonstrated to be valid methods of determining BE. In fact, there is no consensus within FDA that the methods are appropriate. FDA should not finalize the Draft Guidance until sufficient data has been generated to demonstrate that the methods are validated and will ensure that only truly bioequivalent products are approved.

Industry has been particularly outspoken about its concerns with the Draft Guidance during several workshops and meetings in which FDA, academia and Industry participated. During those meetings and still today, those concerns have never been addressed. The Draft Guidance does not address the major scientific concerns of members of AAPS and PhRMA as listed below. These concerns are discussed in

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more detail in the comments we submitted to FDA, Docket 98-D-0388 on the Draft Guidance. A copy of those comments is attached for your convenience.

- Correlation of DPK and clinical safety and efficacy must be demonstrated for each particular class of compounds, each formulation and each indication. None of the studies cited in either the Draft Guidance or discussed at the Expert Panel meeting of August 27, 1999 contained data that showed that differences in DPK capture or reflect significant clinically important differences in formulation.

- Proper validation of the DPK methodology is still outstanding. Data presented in the Draft Guidance failed to validate DPK as a technique that is reproducible for a given investigator and/or for the same drug product. Similar to the formalization of Guidelines for the analysis of plasma samples obtained in oral bioequivalence studies, specific Guidelines outlining the details for validation of both the DPK method and for the analysis of stratum corneum tissue samples must accompany any proposal to use the DPK method as a BE tool.

- On October 23, 1998, Dr. Vinod Shah, Chair, Topical Dermatological Drug Products Working Group to the Joint Advisory Committee, presenting to the Committee on Q1 (qualitative) and Q2 (quantitative) regarding the composition of test and reference products, stated that generics could be approved if *"the product contains **nearly** qualitatively the same ingredients and quantitatively **almost** the same types of composition"* as the innovator. This policy is far too broad.

    - As the Interim Inactive Ingredient Policy was revoked on April 30, 1999 (FR DOC 99-10798), we propose that the Draft Guidance require specifically that Q1 be identical and Q2 be $\pm$ 5%. As the clinical efficacy and safety of topical skin products is a composite of drug and vehicle (excipients), the test and reference product **must** be qualitatively identical (Q1) and quantitatively similar (Q2) $\pm$ 5% in order to assure equivalent clinical results.

    - For Innovator products, addition of any new excipient (change in Q1) or minor changes in excipient levels (Q2) >10% in the Reference product require submission of an NDA, and therefore requires two clinical studies for demonstration of safety and efficacy. In addition, such changes may require additional nonclinical safety studies, i.e. photobiology and photocarcinogenicity. These additional safety concerns are not addressed in the current Guidance. There is no basis to treat generic products differently than innovator products in this context.

We have attached for your review the comments that we submitted to FDA on the Draft Guidance which summarize in detail our significant concerns with the deficiencies of the document.

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Johnson & Johnson continues to support the FDA initiative to determine viable approaches to establishing BE for topical dermatological drug products, and applauds the efforts put into preparing the draft guidance. However, we maintain that it is imperative that all interested parties view any proposed methodology as being scientifically valid and robust. In the absence of new substantiative data, we respectfully reiterate that the Draft Guidance has serious limitations and lacks credibility. We believe our opinion is shared generally by certain members within FDA and by practicing dermatologists, the academic, industrial and government scientific community.

We would be happy to meet with you or any one designated by you to answer any questions that you may have.

Sincerely yours,

Paul F. Manley 9/99

Paul F. Manley
Worldwide Director
Regulatory Affairs